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EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/478,188	Applicant(s) SHEN ET AL.	
	Examiner Kathleen M Kerr	Art Unit 1652	

-- The MAILING DATE of this communication app ars on the cover she t with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-71* is/are pending in the application.

4a) Of the above claim(s) *1-23 and 51-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. Claims 1-71 are pending in the instant application.

Election

2. Applicant's election with traverse of Group 135 in Paper No. 13 is acknowledged. The traversal is on several grounds.

Applicants argue that the restriction within each SuperGroup is legally improper because "an applicant has a right to have ***each claim*** examined on the merits". In the restriction requirement (Paper NOs. 8 and 9), the claims were divided into SuperGroups and Groups. The SuperGroups were drawn to sets of claims relating to similar subject matter (i.e., all DNA claims) ~~yet drawn to different inventions (i.e., ORF1, ORF2, etc.)~~. Thus, the traversal is also on the ground(s) that the restriction between the open reading frames (ORFs), as found in a single claim, is legally improper. Applicants cite *In Re Weber, Soder, and Boksay* saying that the Office cannot restrict within a single claim, irrespective of the Markush-type language. This is not found persuasive. The Examiner reiterates Applicants' citation from *In Re Weber, Soder, and Boksay*:

> If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on its merits. The **totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim**. Further, **since the subgenera would be defined by the examiner rather that the applicant**, it is not inconceivable that a number of the **fragments would not be described** in the specification." (emphasis added)

Firstly, the "fragmentary" claims, as implied by the restriction requirement, taken together **WOULD** be the exactly equivalent in scope to the original, single Claim 1. Claim 1 is drawn to **ANY ONE** of the open reading frames, not to any group or groups of them. Additionally, for claims like Claims 2 and 3 which encompass more than one ORF, Applicants can maintain *exactly* the same scope when said claims are written, for example, as ---A nucleic acid **comprising** ORF 28 and at least one additional ORF---, etc. For such a claim, the search can be limited to ORF 28, provided that not art is identified for ORF 28, to ease the Examiner's search burden while maintaining *exactly* the scope in Applicants' pending claims. Secondly, **APPLICANTS HAVE DEFINED THE SUBGENERA** in both the specification and, most convincingly, in the claims themselves. The Examiner has not divided the claims arbitrarily, but rather has divided the claims as Applicants have described in their specification and as Applicants have *exactly* claimed in their claims which claim "any **one** of C-1027 open reading frames -7 through 42, excluding ORF 9 (cagA)" (emphasis added).

Applicants argue that, no matter how broad, a single generic claim *must* be examined in its entirety. Therefore, the restriction within Claim 1 to any single ORF is improper. This is not found persuasive because Claim 1 is not a single, broad generic claim because no one generic consensus sequence is disclosed to encompass all the ORFs claimed in Claim 1. No broad genus can be searched. The genus/species analogy is only persuasive when a broad genus is claimed and searchable. The argument that ***any claim***, no matter what it encompasses as diverse subject matter, must be examined as a whole is simply unreasonable. If restriction were a matter of claim construction (i.e., no one claim can be restricted into different inventions), why not claim nucleic acid sequences, polypeptide sequences, and methods of use of each of these in the same

claim? Under Applicants' arguments, such a claim would have to be examined together, or at the very least, as a genus/species claim including a "reasonable number" of species. Such a claim is ***not*** commonly proposed because such a single claim would contain MANY DIFFERENT INVENTIONS and would not contain a generic, broad genus that was searchable. This is exactly the case here. Just because the products are all DNA products does not mean that they are any more similar than DNA to protein.

Applicants also argue that particularly restriction within SuperGroup D is improper. Specifically that Claim 26 cannot be examined because it is drawn to methods of using two or more different polypeptides. This argument is not found persuasive because, as the Examiner generally noted above, this claim can be *readily* examined in the restricted Group. Claim 26 is read, in the elected group, as a method using the polypeptide encoded by ORF 28 and at least one additional polypeptide encoded by the C-1027 biosynthesis gene cluster.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-71 are pending in the instant application. Claims 1-23 and 51-71, in their entirety, have been withdrawn from consideration as non-elected inventions. Claims 24-50, as these Claims are drawn to ORF 28, will be examined herein. Claims 24-50, as drawn to methods using an ORF other than ORF 28 (the elected ORF), are withdrawn from consideration as well.

Priority

3. The instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/115,434 filed on January 6, 1999 as requested in the declaration and the first lines of the specification. The Examiner notes that ORF 28, an O-methyltransferase in the C-1027 gene cluster of *Streptomyces globisporus*, does not appear to be disclosed in the provisional

application. Since methods using this ORF are the elected subject matter, none of the claims are granted priority to this date. Thus, the date used for prior art purposes herein is the filing date of the instant application, that is January 5, 2000.

Information Disclosure Statement

4. The information disclosure statement filed on June 26, 2001 (Paper No. 14) has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Drawings

5. The drawings are considered informal for the reasons detailed in the attached copy of PTO Form 948. Appropriate correction is required prior to allowance.

Compliance with the Sequence Rules

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to fully comply with the requirements of 37 C.F.R. § 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

In Figure 7, a consensus sequence is a disclosed that meets the limitations of those sequences and that must be described by sequence identification number. Appropriate amendment to the sequence listing is required to include this consensus sequence.

To be in compliance, applicants must provide a substitute computer readable form (CRF) copy of the "Sequence Listing", a substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d).

Objections to the Specification

7. In the specification, the Title is objected to for not completely describing the claimed subject matter. The Examiner suggests the following new title:

---Methods of Modifying Biological Molecules Using an O-Methyltransferase from C-1027 Biosynthesizing Enzymes---

8. The specification is objected to for being confusing for the following reasons:

~~a) On pages 16-18, Tables I and II~~ cite a relative nucleotide position, but it is unclear which SEQ ID NO these relative positions relate to.

b) On page 29, line 28, the section refers to benzoxazolinates, not beta amino acids.

c) "Epoxide hydrase" and "epoxide hydrolase" are used somewhat interchangeably throughout the specification. If these enzymes are intended to be the same enzyme, consistent claim language is required for clarity.

d) In Table II, ORF 28 is disclosed as being 335 amino acids long since the relative position (46167-47171) contains 1004 base pairs and 1004/3=335 residues. However, in Figure 3B, ORF 28 is described as being 350 amino acids long. The cause for this discrepancy is unclear.

Appropriate correction and/or explanation are required for all of the above points.

9. The amendment filed on December 5, 2001, which amended Table II, contains a deletion in the last line of the original text that is "[102]"; however this text is not replaced and Table II appears to be incomplete. Appropriate correction or explanation is required.

Claim Objections

10. Claims 24-50 are objected to for containing non-elected subject matter. Applicants elected Group 135 drawn to Claims 24-50 as said claims relate to ORF 28. As found in Table II, ORF 28 encodes an O-methyl transferase in the C-1027 gene cluster as flanked by primers SEQ ID NOs: 73 and 74. The DNA encoding ORF 28 is within SEQ ID NO:2, 4188-5189 base pairs. Claims 24-50 will be examined has written or as considered below with respect to elected subject matter.

a) Claim 24, as if it were drawn to a method of chemically modifying a biological molecule using the polypeptide encoded by ORF 28.

b) Claim 25, as drawn to an O-methyl transferase.

c) Claim 26, as drawn to using the polypeptide of ORF 28 and at least one additional C-1027 polypeptide.

d) Claim 27, as drawn to using the polypeptide of ORF 28 and at least two additional C-1027 polypeptides.

e) Claims 41-50, as drawn to using the ORF 28 polypeptide **and additionally** any or all of the Markush members in Claims 41-50.

Appropriate amendment to the claims to claim only elected subject matter is required.

11. Claim 25 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 25 merely identifies the function of the polypeptide of ORF 28 as O-methyltransferase. However, this is an inherent feature in the polypeptide of ORF 28 and, thus, cannot further limit the claimed subject matter.

12. Claims 26-27 are objected to for using improper verb tenses. In Claims 26 and 27, both in line 1, the term "comprising" should be ---comprises---.

13. Claim 30 is objected to for improper English. The verb ---is--- should be inserted before "*ex vivo*".

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14. Claim 32 is objected to for improper English. The adjective "exogenous" should be replaced by an adverb ---exogenously---.

15. Claim 36 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The limitation of Claim 36, requiring the host cell to synthesize deoxysugar, does not further limit the parent claim because all cells synthesize deoxysugars.

16. Claim 39 is objected to as a duplicate claim of Claim 30.

17. Claim 40 is objected to for improper English. In line 2, the word ---least--- should be inserted before ---substantially---.

18. Claim 41 is objected to for a typographical error. In line 2, the word "polyeptide" is misspelled.

19. Claims 41-42 are objected to for a typographical error. The word "sulfer" is misspelled in both claims; the correct spelling is ---sulfur---.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claims 24-50 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 24, line 3, the phrase "a C-1027 biosynthesis gene cluster open reading frame" is confusing as to its metes and bounds; this phrase is seen throughout the instant claims. The specification discloses a particular C-1027 gene cluster with a specific ORF 28 (the elected subject matter). As disclosed, ORF 28 encodes an O-methyl transferase ORF in the C-1027 gene cluster as flanked by primers SEQ ID NOs: 73 and 74. The DNA encoding ORF 28 is within SEQ ID NO:2, 4188-5189 base pairs. However, the specification also defines the C-1027 gene cluster as any enediyne-synthesizing gene cluster from other organisms. Are these claims limited to the polypeptide encoded by SEQ ID NO:2, 4188-5189 base pairs, or can

the claims read on an O-methyltransferase from any enediyne-synthesizing organisms? Clarification is required.

In Claims 43-44, reference to particular ORFs is also confusing for the reasons cited above for the entire gene cluster and its specificity.

21. Claim 40 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "substantially" in claim 40 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear which polypeptides are include – all those in Tables I, II, and III? Just Tables I and II? Clarification is required.

22. Claim 40 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "enediyne analogue" is unclear. How similar must a compound be to an enediyne compound to be considered and analogue? Is the chromophore sufficient? Is the protein sufficient? How similar to either of these structures must the claimed analogue be?

23. Claims 41-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claims 41 and 42, the term "hydrase" is unclear. As noted above,

"epoxide hydroxylase" and "epoxide hydrase" are used inconsistently throughout the specification. Consistent language, particularly in the claims, is required.

24. Claims 41-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claims 41 and 42, the requirement for "proline oxidase" is wholly unclear since this function does not appear in Tables I, II or III that are the proposed functions of the polypeptides encoded by the C-1027 gene cluster.

25. Claims 41-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claims 41 and 42, the following references are found: "an epoxide hydrase", "a monooxygenase", "an iron-sulfur flavoprotein", "a p-450 hydroxylase", "an oxidoreductase, and "a proline oxidase". The article "an" or "a" indicates any; thus more than one of each of these enzyme types *must* be found in the specification. Only ORF 17 is described as an epoxide hydroxylase. ORFs 4 and 20 are loosely considered monooxygenases; however, ORF 4 is actually a chlorophenol-4-monooxygenase. Is ORF 4 included? Only ORF 21 is described as an Fe-S flavoprotein. Two p-450 hydroxylases are described; can either be used? Many enzymes from Tables I and II fall into the category of oxidoreductase; is this limitation limited to those noted as oxidoreductases, such as ORFs 30, 32, and 38? Is ORF 35, an oxidase/dehydrogenase also considered? No proline oxidase is described. If the "unknown proteins" disclosed in the tables result as one of these categories, are they included as well? Thus, the metes and bounds of the scope of the instant claims are unclear.

26. Claim 45 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The purpose of the limitation of ORF 3 is already found in the parent claim, Claim 44. The addition of the limitation is unclear.

27. Claims 46-50 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 46-49 contain references to enzyme names, just as found in Claims 41 and 42 rejected above. The same arguments, concerning which ORFs are included, are set forth against Claims 46-50 here. The confusing nature of the article "a" when only a single type of the enzyme is described in the specification is also noted as set forth above for Claims 41-45. Thus, the metes and bounds of the scope of the instant claims are unclear.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

28. Claims 24-50 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are directed to methods of chemically modifying biological molecule by contacting said biological molecule

and a polypeptide encoded by ORF 28 from an enediyne biosynthetic gene cluster; the breadth of "enediyne gene cluster" instead of C-1027 gene cluster results from the definition in the specification as noted above in a 35 U.S.C. § 112, second paragraph rejection of the claims. While the specification adequately describes such methods using the O-methyltransferase from ORF 28 of the C-1027 biosynthetic gene cluster (specifically, SEQ ID NOs: 1 and 2) and a 3,5-dihydro-anthranilate shown as the O-methyltransferase substrate in Figure 3B, the specification does not adequately describe other O-methyltransferases from other enediyne gene clusters as well as using other biological molecules as substrates.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of methods using proteins or genetic material, which are chemical compounds, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, one species of the claimed genus of methods is fully described. However, this species does not predictably identify either the structure of specific

function of other members of the genus. Particularly, polypeptides from other enediyne-synthesizing organisms, wherein said polypeptides are analogous to ORF 28, cannot be predicted from the disclosed ORF 28 in either their structure or function. While the structure may be similar, it will not be identical and variations cannot be predicted. While the function may be similar, it will not be identical using a different substrate to produce a different product. Thus, the ability of the ORF 28 disclosed to predict other ORF 28 polypeptide is low. Therefore, the single disclosed species of the genus of methods claimed does not adequately describe the genus.

29. Claims 24-27, 30, 37, 39, 40-50 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for *ex vivo* methods using only the O-methyltransferase, does not reasonably provide enablement for *ex vivo* methods using more than one enzyme from the gene cluster. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The instant claims are drawn to methods of biosynthesis using a naturally *in vivo* system; this system is very complex involving many interacting proteins and their products. The ability to use a single enzyme from this pathway *ex vivo* is enabled considering the extensive skill in the art of protein expression and activity assays. However, the ability to express and utilize the entire gene cluster, with its expressed proteins retaining their activities *ex vivo,* would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue

experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The quantity of experimentation necessary to express the entire gene cluster, purify the proteins, and reconstitute the system *ex vivo* would be copious. The specification present no guidance or working examples for such experimentation. The nature of the invention is a complex system of assembly-line-type enzymes that function together to produce a final complex compound; moreover, the exact functions and sequence of reactions is not wholly understood. The ability to predict the functionality of the claimed methods to the full extent of their scope is minimal.

Claim Rejections - 35 U.S.C. § 101

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

30. Claims 24-27, 38, 40-50 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The methods of modifying a biological molecule using a polypeptide encoded by the C-1027 gene cluster are methods which naturally happen since *S. globisporus* naturally produces C-1027 through a given set of biosynthetic reactions including those claimed. The hand-of-man has not been incorporated into the instant claim language. Thus, the instant claims read on natural events that are non-statutory subject matter.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

31. Claims 24-27, 38, 40-50 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hu *et al.* (IDS #14 reference 10). The instant claims are drawn to methods of modifying a biological molecule using polypeptides of the C-1027 biosynthetic gene cluster in a bacterial cell.

Hu *et al.* teach that *Streptomyces globisporus* strain C-1027 naturally produces the antibiotic C-1027 that is a potent cytotoxicity agent (see Abstract). While Hu *et al.* teach that *S. globisporus* is wholly responsible for the synthesis of C-1027, Hu *et al.* do not teach, *per se*, the methods of using the polypeptides within the strain to chemically modify the C-1027 substrates.

At the time of the invention, it would have been obvious for one of ordinary skill in the art to combine the teachings of Hu *et al.* with general knowledge of the art to comprehend and reduce to practice the claimed methods since Hu *et al.* performed such methods without direct intent. One would have been motivated to use *S. globisporus* C-1027 to produce its product, antibiotic C-1027, thereby practicing the claimed methods, because antibiotic C-1027 is useful in the study of novel antibiotics and cancer therapeutics. One would have had a reasonable expectation of success that the cultivation of *S. globisporus* would produce the antibiotic C-1027 and practice the claimed methods because the cultivation is described directly by Hu *et al.*

Double Patenting

32. Applicant is advised that should claim 30 be found allowable, claim 39 will be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See M.P.E.P. § 706.03(k).

Conclusion

33. Claims 24-50 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Kathleen Kerr
March 16, 2002